Electronic supplementary material.

Mathematical model for VZV transmission and reactivation, parameterization, and details on the optimal control problem.

Index

1. The age-structured model for VZV, parameter assignments, and structure of the optimal control problem.

1.1 Dynamic equations used in the optimal control problem.

The baseline age structured model for VZV used in the optimal control analyses reported in the main text describes VZV transmission and reactivation within a demographically stationary population with a constant number of births *B* per year, and an age-specific mortality schedule summarized by an age-specific mortality rate μ_i representing the hazard of death per unit of time in each age group. The epidemiological component of the model includes age heterogeneities in the processes of varicella transmission, boosting of CMI, and reactivation of VZV into herpes zoster (HZ). In particular age-heterogeneities in transmission and boosting are represented through an age-specific contact matrix C=[C_{ij}] whose generic element denotes the average number of contacts that an individual in age group *i* has with individuals in age group *j* per unit of time.

The model is described by ordinary differential equations [1]. We consider 5-yrs age groups, with maximal age set to 80 years. Age-transitions between age groups are governed by age-specific transfer rates whose magnitude is given by the reciprocal of the age group size [1,2].

The baseline model includes eleven epidemiological compartments (176 equations in total). The epidemiological transitions considered are as in similar models for VZV transmission and reactivation [3–5] and are depicted in Fig. 1. The model splits the population in two subpopulations: the subpopulation of unvaccinated individuals and the subpopulation of vaccinated individuals, i.e. those who have been successfully immunized (at birth) against varicella by a perfect vaccine. This hypothesis was made for reasons of parsimony, i.e. to avoid the inclusion of complications, namely breakthrough varicella infection following from vaccine imperfections, which are of little relevance for the conclusions of the present work. The varicella vaccine uptake at birth, denoted by *u(t)*, allocates individuals in the two “arms” of the model.

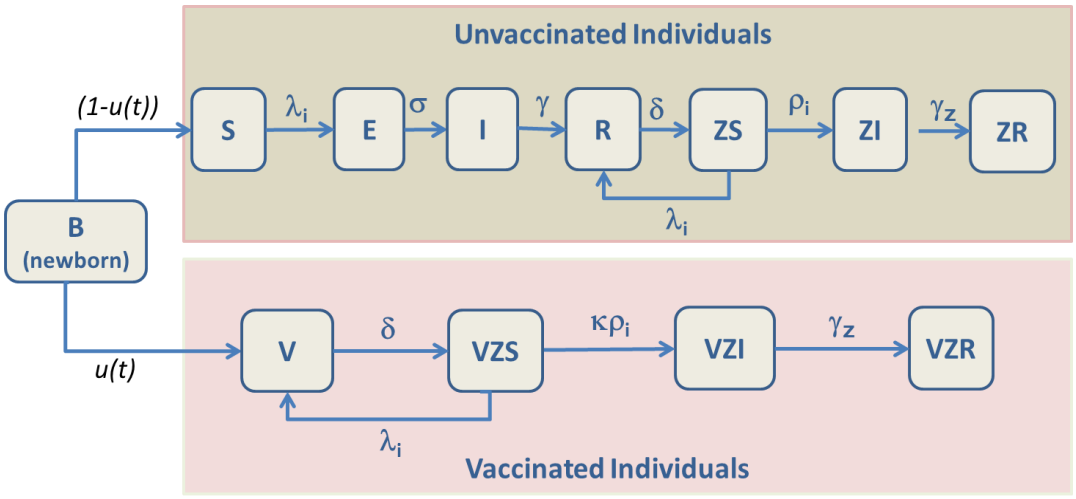

Fig. 1. Flow diagram of epidemiological transition in the key model.

The dynamical equations for the baseline model are reported in the table below. The corresponding demographic and epidemiological parameters are described in a subsequent table.

Unvaccinated compartments $S_1'(t) = B(1-u(t)) - (\mu_1 + ag_1 + \lambda_1(t))S_1(t)$ $S_i'(t) = ag_{i-1}S_{i-1}(t) - (\mu_i + ag_i + \lambda_i(t))S_i(t) \quad i = 2,\ldots, m$ $E_i'(t) = ag_{i-1}E_{i-1}(t) + \lambda_i(t)S_i(t) - (\mu_i + ag_i + \sigma)E_i(t)$ $I_i'(t) = ag_{i-1}I_{i-1}(t) + \sigma E_i(t) - (\mu_i + ag_i + \gamma)I_i(t)$ $R_i'(t) = ag_{i-1}R_{i-1}(t) + \gamma I_i(t) + \lambda_i^B(t)ZS_i(t) - (\mu_i + ag_i + \delta)R_i(t)$ $ZS_i'(t) = ag_{i-1}ZS_{i-1}(t) + \delta R_i(t) - (\mu_i + ag_i + \lambda_i^B(t) + \rho_i)ZS_i(t)$ $ZI_i'(t) = ag_{i-1}ZI_{i-1}(t) + \rho_i ZS_i(t) - (\mu_i + ag_i + \gamma_Z)ZI_i(t)$ $ZR_i'(t) = ag_{i-1}ZR_{i-1}(t) + \gamma_Z ZI_i(t) - (\mu_i + ag_i)ZR_i(t)$	$S_i(t)$, $E_i(t)$, $I_i(t)$, $R_i(t)$= numbers of individuals in age group i who are respectively susceptible to varicella (S), varicella exposed (E), varicella infective (I), and removed from varicella(R) at time t; $ZS_i(t)$, $ZI_i(t)$, $ZR_i(t)$ = numbers of individuals in age group i who are respectively susceptible to HZ (ZS), zoster infective (ZI), and removed from zoster compartment (ZR) at time t;
Vaccinated compartments $V_1'(t) = B \cdot u(t) + \lambda_1^B(t)VZS_1(t) - (\mu_1 + ag_1 + \delta)V_1(t)$ $V_i'(t) = ag_{i-1}V_{i-1}(t) + \lambda_i^B(t)VZS_i(t) - (\mu_i + ag_i + \delta)V_i(t) \quad i = 2,.., m$ $VZS_i'(t) = ag_{i-1}VZS_{i-1}(t) + \delta V_i(t) - (\mu_i + ag_i + \lambda_i^B(t) + \rho_i)VZS_i(t)$ $VZI_i'(t) = ag_{i-1}VZI_{i-1}(t) + \rho_i VZS_i(t) - (\mu_i + ag_i + \gamma_Z)VZI_i(t)$ $VZR_i'(t) = ag_{i-1}VZR_{i-1}(t) + \gamma_Z VZI_i(t) - (\mu_i + ag_i)ZR_i(t)$	$V_i(t)$ = numbers of individuals in age group i who have been successfully immunized against varicella (and temporary unsusceptible to HZ).$VZS_i(t)$, $VZI_i(t)$, $VZR_i(t)$ = numbers of varicella vaccinated individuals in age group i who are respectively susceptible to HZ (VZS), zoster infective (VZI), and removed from zoster disease (VZR) at time t;

Tab. 1. Equations of the baseline age-structured model and explanations for related dynamic variables.

The quantities $\lambda_i(t)$ and $\lambda_i^B(t)$ respectively represent the force of varicella infection (FOI) and the force of CMI boosting (FOB). For the sake of simplicity we assume a negligible contribution from zoster infective subjects to the varicella FOI as based on both empirical data [6] and modeling studies [3] documenting that HZ is much less infectious than varicella. Moreover we make the assumption of *full CMI boosting*, according to which the FOI and the FOB are assumed to be identical, as hypothesized in much of the modelling literature [3,7,8]. Consequently:

$$\lambda_i(t) = \lambda_i^B(t) = q\sum_{j=1}^{m} C_{ij} \cdot \frac{I_j(t)}{N_j(t)}$$

where C_{ij} denotes the average number of contacts that an individual in age group *i* has with individuals in age group *j* per unit of time, q represents a transmission coefficient per single contact, and the ratio $I_j(t)/N_j(t)$ the varicella infective prevalence per unit of population. The transmission coefficient *q* is assumed to be age-independent, following the so called social-contact hypothesis [9].

The age-specific rate of VZV reactivation into herpes zoster was specified according to the following form (*a* denotes age):

$$\rho(a) = \rho_0 + \pi \cdot a^{\eta} \qquad (\rho_0, \pi, \eta) > 0$$

The previous form amounts to assume that the age-specific reactivation rate is the sum of a constant component, and of and age-dependent power-type (or Weibull-type), component, mimicking senescence effects. This form is slightly simplified but more parsimonious compared to other forms adopted in the VZV modeling literature based on the hypothesis of full temporary immunity to HZ ([3–5]).

We have also considered a simple extension of the baseline model to include also vaccination against HZ as a sensitivity factor. In this model we assume that the HZ vaccine is perfect one, so that all HZ vaccinated individuals are removed. The HZ vaccine is administered irrespective to all compartments unless in the

presence of varicella infection (compartments E,I), or of zoster infection (compartments ZI, VZI), or of zoster history (compartments ZR,VZR). The HZ vaccine is administered in a fixed proportion to individuals of the target age, moving them into the HZ vaccine compartment.

1.2. Parameters of the age-structured model

Definitions, dimensional units, assignments, and literature sources for all parameters of the VZV model used in the main text, and for all relevant control parameters are summarized in Tab.1. Sensitivity analyses of model responses to epidemiological parameters are available on request.

Parameters	***Unit***	***Role***	***Range or value***	***Source***
T = length of control horizon	*Year*	*Free simulation parameter*	*[20,100]*	---
c_Z = relative cost of a zoster case with respect to a varicella case	-	*Free simulation parameter*	*[1, 50]*	[10–12]
r = discount rate	yr^{-1}	*Fixed r=0 (no discount)*	*0.03*	[10,11]
G= "weight" augmented integral	-	*Free simulation parameter*		---
μ_i = mortality rate in age group i	yr^{-1}	*Fixed*	*1/75*	UN Italian life table 2005-2010
ag_i = transfer rate from age group i to age group (i+1)	yr^{-1}	*Fixed*	*0.2*	---
$C=[C_{ij}]$=contact matrix.	yr^{-1}	*Fixed*	---	Polymod matrix of total contacts for Italy [13]
q= transmission coefficient (per contact) of varicella infection	-	*Fixed*	*0.0338*	Fitted to Italian serological data [17]
σ = rate of development of varicella infective phase	yr^{-1}	*Fixed*	*26*	[14].
γ = varicella recovery rate	yr^{-1}	*Fixed*	*52*	[14].
δ = rate of decay of CMI protection.	yr^{-1}	*0.05*	*0.05*	[3]
ρ_i = rate of development of natural HZ for individuals in age group i	Yr^{-1}	*Fixed*	ρ_0*=0.0046;* π*= 0.7208e-06 ;* η *=2.2904*	Fitted to Italian HZ incidence data [19]

Parameters	*Unit*	*Role*	*Range or value*	*Source*
γ_Z = zoster recovery rate	yr^{-1}	*Fixed*	*52*	[14].
k = reduction factor of zoster risk for varicella vaccinated individuals	-	*Fixed*	*0.125*	[15]

Tab. 1. Parameters of the age-structured model (definitions, range, sources).

1.3 Parameterization of the age-structured model.

The age-structured model has been parameterized using real data from Italy. The age-specific mortality rate has been drawn from the average abridged (5-years age groups) Italian life-table for the period 2005-2010 (source UN 2015). This yields a life expectancy e_0 equal to about 75 years (smaller than the actual life expectancy due to the truncation of the model population at the maximal age of 80 years). The total population size P is set to 60 million to coarsely mimic the current size of the Italian population. The number of births per year B is then computed through the known formula (valid in stationary populations) $B=P/e_0$. As for the contact matrix C we have used the "Polymod" matrix of total reported contacts for Italy [13]. The corresponding transmission coefficient q has been estimated by maximum likelihood by fitting an age-specific SIR model for varicella based on the assumption of demographic and epidemiological equilibrium to available Italian VZV serological data (documenting age-specific acquisition of immunity to varicella infection) from the pre-vaccination period [16], . The ensuing best estimate of the transmission coefficient was q=0.03381 (see Table 1). The corresponding value of the basic reproduction number of varicella - representing the average number of secondary varicella cases of infection caused by a single infective case when introduced in a wholly susceptible population with age-specific contact patterns determined by the contact matrix C [17] – was R_0=5.19. Finally, the age-specific rate $\rho(a)$ of VZV reactivation into herpes zoster was estimated by fitting the entire model above for the unvaccinated compartments (still under the hypothesis of epidemiological equilibrium), to data on age-specific incidence of herpes zoster in Italy [18]. In this case the FOI was set to its best estimate found from the fit to serological data, and only the parameters of the zoster reactivation rate $\rho(a)$ were estimated from data.

1.4 Structure of the optimal control problem

Based on the stated hypotheses and parameters the baseline optimal control problem (section 2 of main text) considers the cost functional:

$$C_{[0,T]} = \sum_{i=1}^{m} \left(\int_0^T e^{-rt} \left(\sigma \cdot E_i(t) + c_Z \rho_i \cdot ZS_i(t) + c_Z k \rho_i VZS_i(t) \right) dt \right)$$

The extension to the augmented cost functional is trivial.

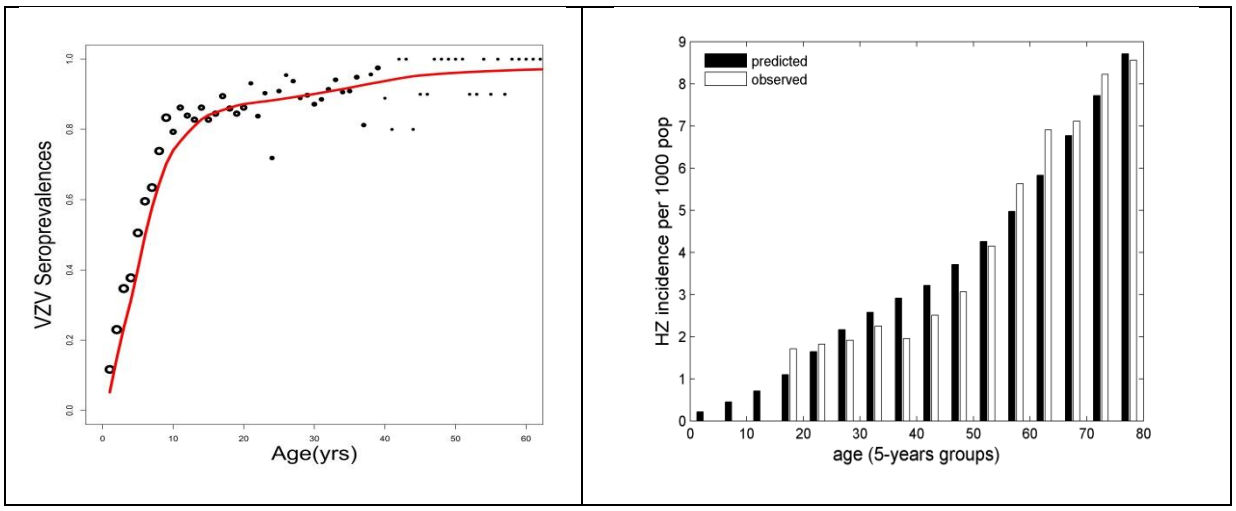

Fig. 2. Fit of the age-structured model to Italian VZV data. Left panel: fit to varicella seroprevalence data by age. Right panel: fit to HZ incidence, by age (note that no data are available prior to age 15, see [19]).

2. Details on the computation of solutions of the optimal control problem.

The optimal program is performed to minimize the adopted cost functional over the whole planning horizon *[0,T]*. The control function, i.e. the vaccination coverage u(t), is allowed to vary between 0% (no vaccination) and a maximum feasible coverage of 90%, i.e. in excess of the critical coverage predicted by the model considered, in order to allow greater flexibility. The optimality system is solved numerically and the solution is obtained, at each sampling time, using Matlab [19] nonlinear constrained minimization routine *fmincon*. To cope with local minima problems, a pool of 15 sets of initial conditions has been

created as different starting points for the optimization algorithm. The first five initial conditions have been generated assuming constant vaccination coverages (10%,30%,50%,70%, 90% respectively) overall the time horizon, while in the remaining ten cases the initial values of the optimization parameters have been randomly chosen. The optimal coverage was eventually chosen as the one associated to the minimum value of the cost function among those obtained for the whole pool of initial conditions.

3. Logistic coverage functions.

In the main text we considered logistic control functions as an instance of "feasible" coverage functions allowing a gradual, instead than abrupt, decline of the boosting intensity, by maintaining some temporary VZV circulation. The form adopted for the logistic coverage function is the following:

$$u_l(t) = \frac{a}{1 + b \cdot e^{-ct}} + d \quad t > 0; a > 0, b > 0, c > 0, d > 0$$

Details about the optimization ranges for the parameters (*a,b,c,d*) of the logistic control function are reported in the following table:

	a	*b*	*c*	*d*
Lower Bound	*0*	*0.1*	*0.01*	*0*
Upper Bound	*0.9*	*+∞*	*100*	*0.9*

4. Further results on free optimization.

For sake of completeness and comparison we report here outputs of free optimization for different length of the horizon (*T=20 yrs, T=30*, also reported in the main text, *T=50 yrs*).

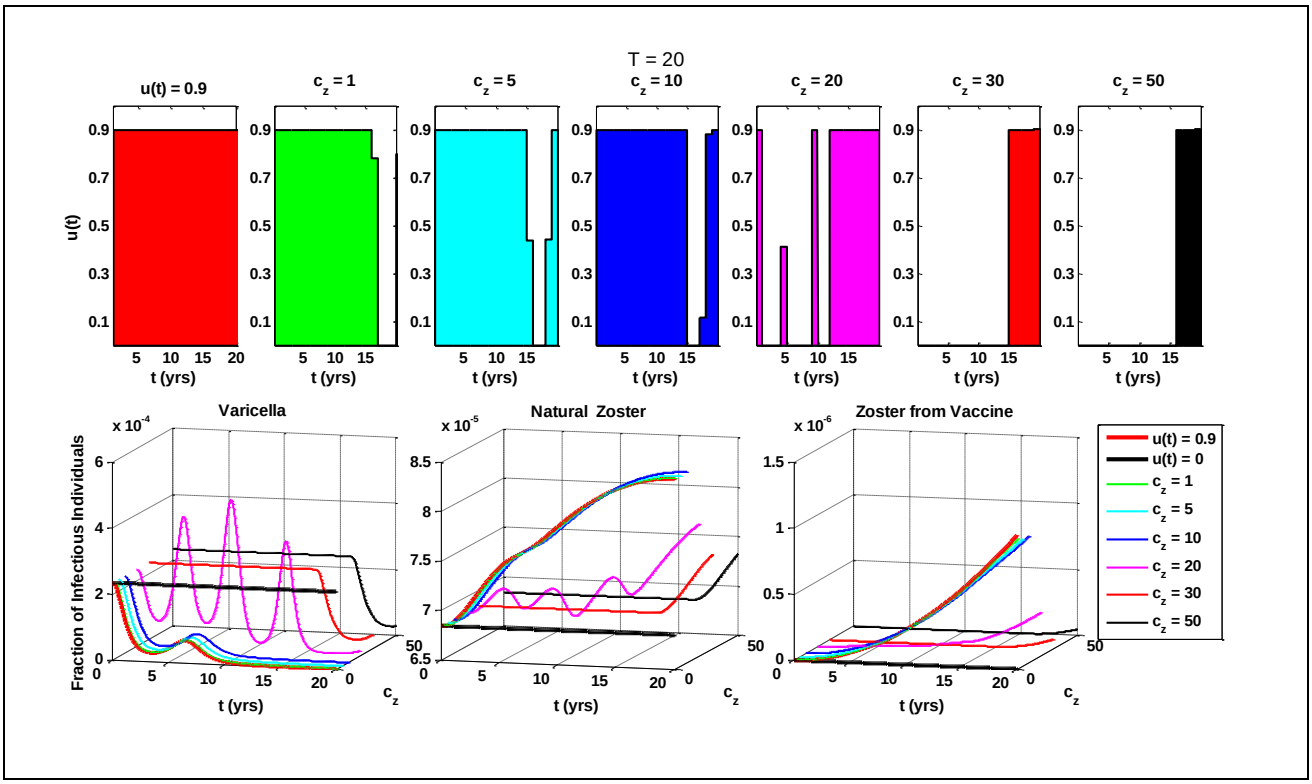

Fig. 3. The free problem for T=20y and different relative HZ costs. Top: trends of the optimal coverage as functions of time (t). Bottom: temporal trends of varicella cases (left), natural HZ cases (center), and vaccine-related HZ cases (right). Cases of a constant vaccine uptake set at the maximal level allowed (0.9), and without any immunization, also reported.

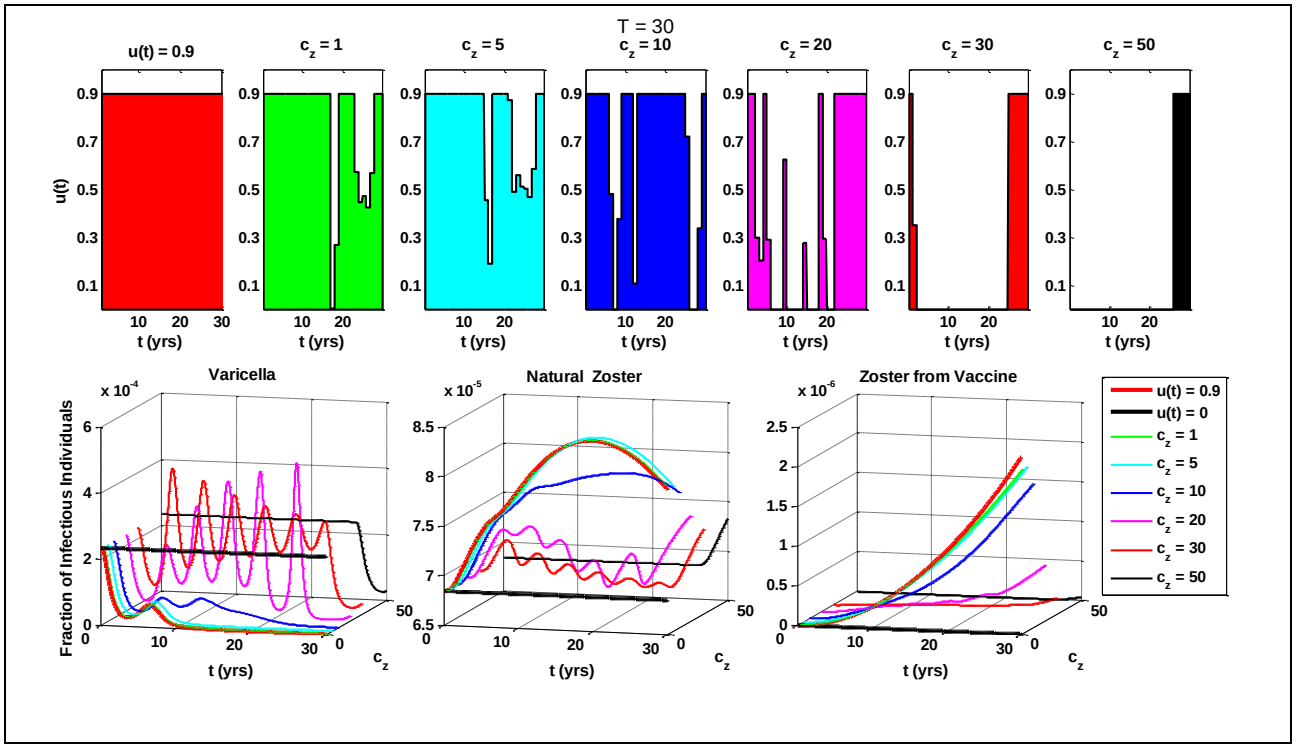

Fig. 4 The free problem for T=30y and different relative HZ costs. Top: temporal trend of the optimal coverage. Bottom: temporal trends of varicella cases (left), natural HZ cases (center), and vaccine-related HZ cases (right). Cases of a constant vaccine uptake set at the maximal level allowed (0.9), and without any immunization, also reported.

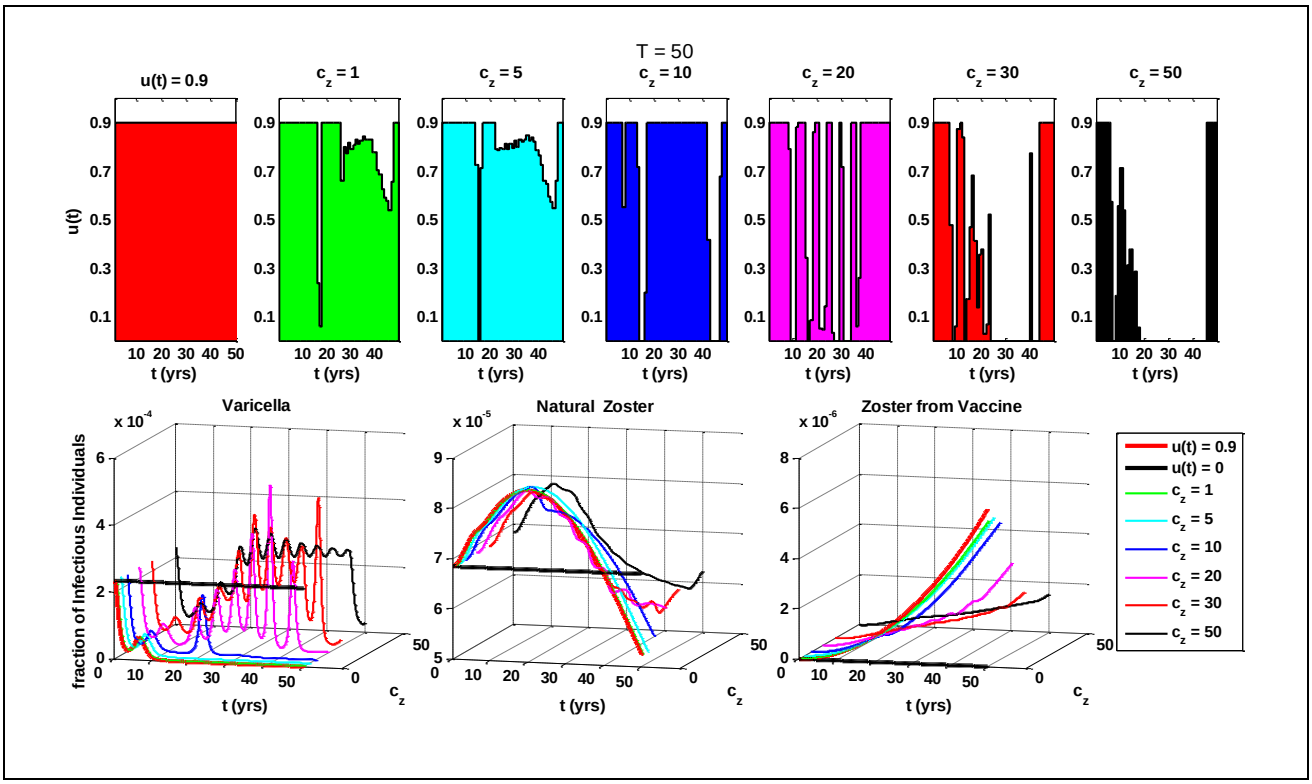

Fig. 5. The free problem for T=50y and different relative HZ costs. Top: temporal trend of the optimal coverage. Bottom: temporal trends of varicella cases (left), natural HZ cases (center), and vaccine-related HZ cases (right). Cases of a constant vaccine uptake set at the maximal level allowed (0.9), and without any immunization, also reported.

5. Further results on logistic optimization.

We report in full detail the results on the logistic optimization for different lengths *T* of the horizon (*T*=25, 30, 35, 40, T=45, T=50, T=70, *T*=100 yrs) over the whole grid of values (from 1 to 50, see Table 1 above) of the relative cost of HZ. The figure includes also the case *T*=30 reported in the main text.

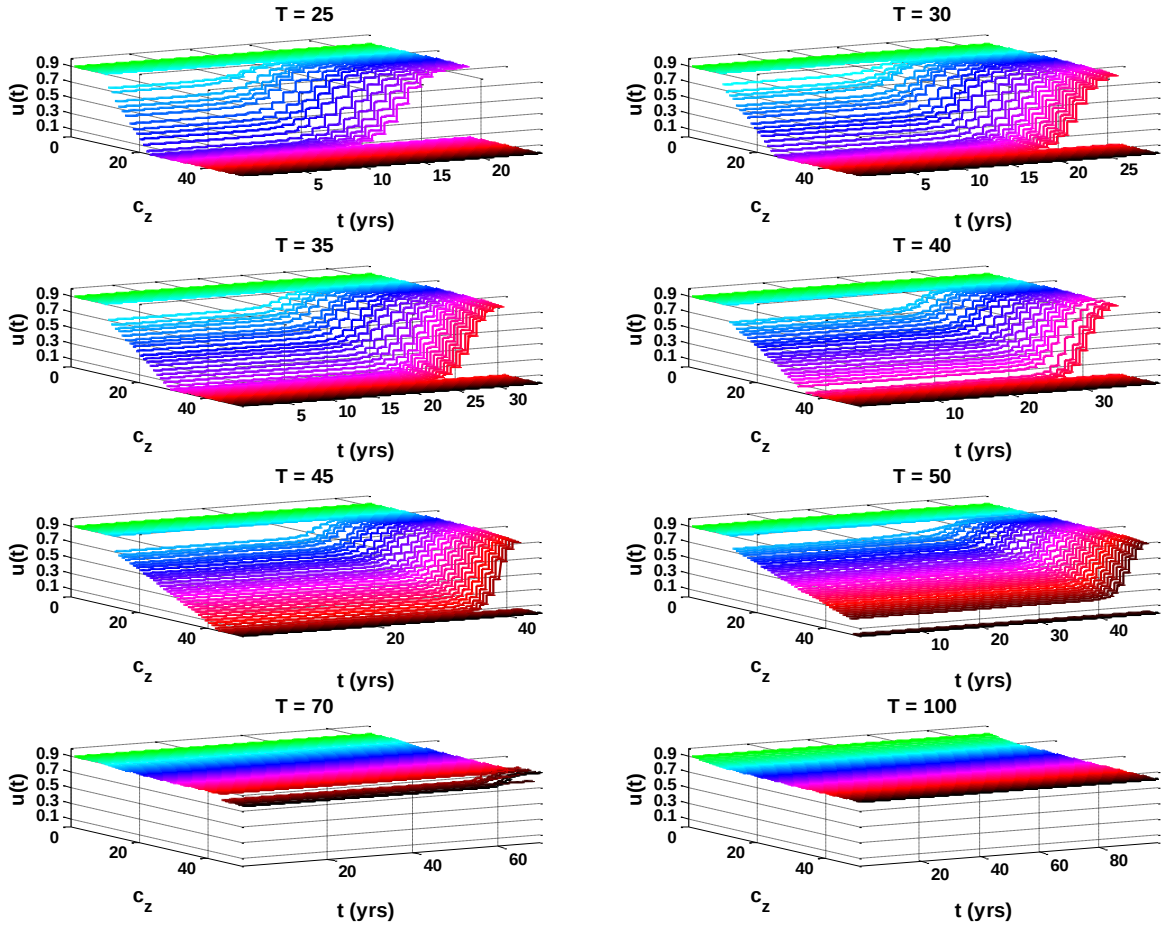

Fig. 6. The case of logistic optimization. Optimal varicella coverage path for different lengths T of the horizon over the whole grid of values of the relative cost of HZ reported in Table 1.

6. Logistic optimal control paths of varicella vaccine uptake under some background HZ vaccination.

In this section we report some details on the sensitivity analysis carried out to check how the optimal control paths of the varicella vaccine uptake are affected by the presence of some degree of exogenous vaccination against HZ. In this case the optimal control strategy aims to control the "residual" costs arising from varicella cases and residual HZ cases from individuals who have not been immunized against HZ. For simplicity we assume that HZ immunization initiates at the same time of varicella immunization.

We have hypothesized a perfect HZ vaccine, i.e. characterized by 100% take and lifelong duration, and have considered a number of alternative HZ coverage schedules depending on two factors, namely the target age at immunization (taken either as 60, 50, or 20 years) and the proportion immunized p_{HZ} (set to 20%, 40%, or 60% respectively). This simplistic hypothesis seems able to provide a neater response, at least from our perspective, compared to the use of estimates from the available literature which shows a number of drawbacks. Indeed there is, to our knowledge, only one attempt ([4]) to estimate the characteristics of the HZ vaccine based on the clinical trials data [20]. This study provides (see also the Supplementary Materials of their paper) estimates of the vaccine take but only for the age groups for which the vaccine had been licensed (60-64,65-69, etc) while in this experiment we also want to consider ages below the minimum currently considered for immunization. Moreover these estimates are conditional on the hypothesis made on the duration of the vaccine protection (set to 20 yrs), and are somewhat dependent on the hypothesized average duration of CMI immunity offered by boosting. In particular the figure of 20 yrs regarding the duration of HZ vaccine protection is somewhat in contradiction with the current official indication of the CDC-US stating that: "In people vaccinated at 60 years old or older, vaccine efficacy wanes within the first 5 years after vaccination, and protection beyond 5 years is uncertain." (see: http://www.cdc.gov/vaccines/vpd-vac/shingles/hcp-vax-recs.html).

Inclusion of the "extreme" age of 20y was motivated by the fact that varicella vaccinated individuals might, in a situation of sustained immunization, develop susceptibility to herpes zoster much earlier compared to

a pre-vaccination situation. Feeling of the relevance of this comparison is reported in the two figures below (Fig. 7, Fig. 8) which report the temporal trend of natural and vaccine-related HZ for two distinct scenarios where varicella immunization at birth (with actual coverage set at the constant level of 60%) and zoster immunization are initiated at the same time (t=100 yr) from a regime of pre-vaccination equilibrium. In particular Fig. 7 consider the case of "late" HZ immunization (at the age of 60 years) while Fig. 8 consider the case of "early" HZ immunization (at the age of 20 years). As clear from the graphs in Fig. 7, late HZ immunization is effective in mitigating the natural zoster boom –because susceptible individuals to natural HZ are mostly concentrated at high ages, but not in mitigating HZ in varicella vaccinated individuals, which become susceptible to HZ much earlier. On the other hand, as clear from Fig. 8, early HZ immunization (age =20 yrs) is not effective in mitigating the natural HZ boom but it is in mitigating HZ in varicella vaccinated individuals.

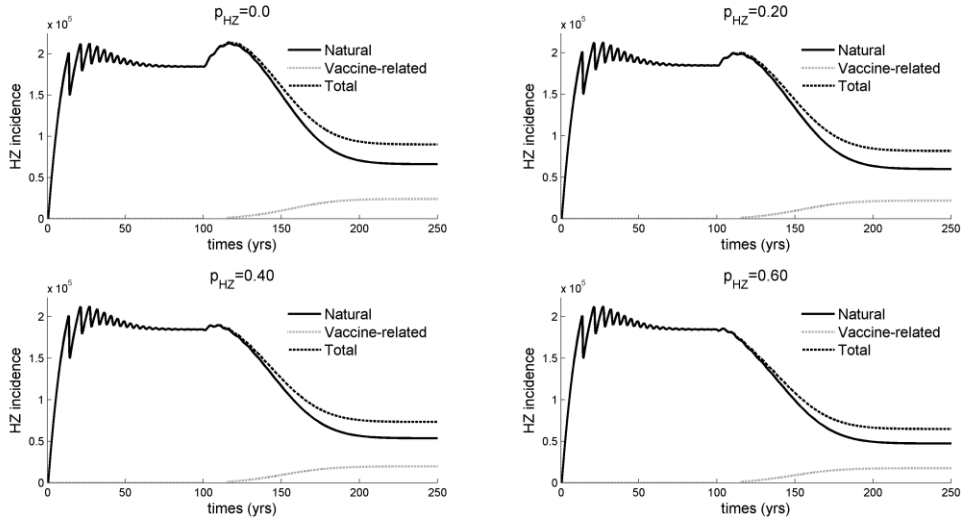

Fig. 7. Temporal trend of natural and vaccine-related HZ under a joint varicella and HZ immunization program initiating at time t=100 years from a condition of pre-vaccination equilibrium. Varicella immunization is administered at birth (with actual coverage set at the constant level of 60%). The age at zoster vaccination is set to 60 years. Different HZ coverage levels have been considered (p_{HZ} =0, 0.20, 0.40, 0.60).

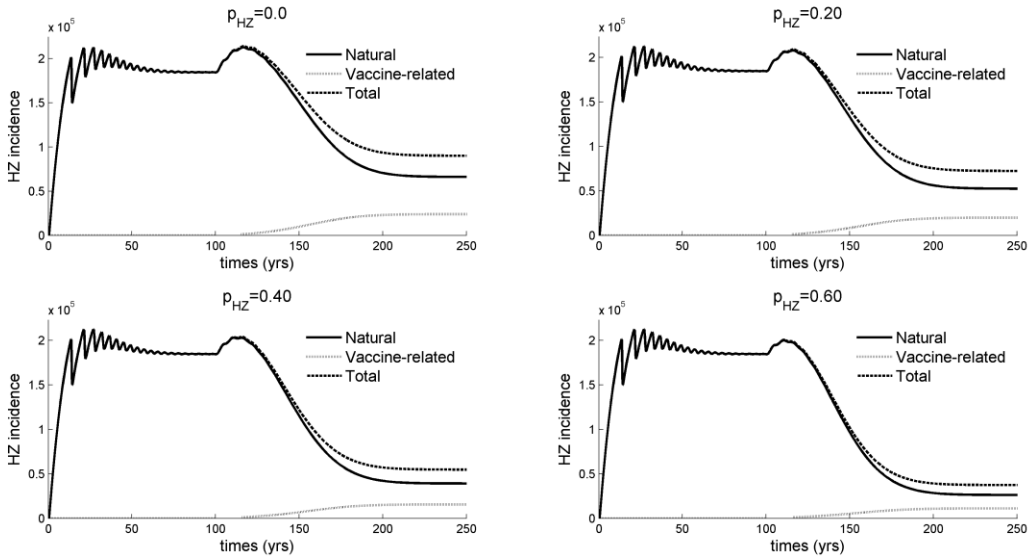

Fig. 8. Temporal trend of natural and vaccine-related HZ under a joint varicella and HZ immunization program initiating at time t=100 years from a condition of pre-vaccination equilibrium. Varicella immunization is administered at birth (with actual coverage set at the constant level of 60%). The age at zoster vaccination is set to 20 years. Different HZ coverage levels have been considered (p_{HZ} =0, 0.20, 0.40, 0.60).

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